UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

Note to Reader
August 7, 1998

Background: As part of its effort to involve the public in the implementation of the Food Quality Protection Act of 1996 (FQPA), which is designed to ensure that the United States continues to have the safest and most abundant food supply, EPA is undertaking an effort to open public dockets on the organophosphate pesticides. These dockets will make available to all interested parties documents that were developed as part of the U.S. Environmental Protection Agency's process for making reregistration eligibility decisions and tolerance reassessments consistent with FQPA. The dockets include preliminary health assessments and, where available, ecological risk assessments conducted by EPA, rebuttals or corrections to the risk assessments submitted by chemical registrants, and the Agency's response to the registrants' submissions.

The analyses contained in this docket are preliminary in nature and represent the information available to EPA at the time they were prepared. Additional information may have been submitted to EPA which has not yet been incorporated into these analyses, and registrants or others may be developing relevant information. It's common and appropriate that new information and analyses will be used to revise and refine the evaluations contained in these dockets to make them more comprehensive and realistic. The Agency cautions against premature conclusions based on these preliminary assessments and against any use of information contained in these documents out of their full context. Throughout this process, if unacceptable risks are identified, EPA will act to reduce or eliminate the risks.

There is a 60 day comment period in which the public and all interested parties are invited to submit comments on the information in this docket. Comments should directly relate to this organophosphate and to the information and issues

available in the information in this docket. Once the comment period closes, EPA will review all comments and revise the risk assessments, as necessary.

These preliminary risk assessments represent an early stage in the process by which EPA is evaluating the regulatory requirements applicable to existing pesticides. Through this opportunity for notice and comment, the Agency hopes to advance the openness and scientific soundness underpinning its decisions. This process is designed to assure that America continues to enjoy the safest and most abundant food supply. Through implementation of EPA's tolerance reassessment program under the Food Quality Protection Act, the food supply will become even safer. Leading health experts recommend that all people eat a wide variety of foods, including at least five servings of fruits and vegetables a day.

Note: This sheet is provided to help the reader understand how refined and developed the pesticide file is as of the date prepared, what if any changes have occurred recently, and what new information, if any, is expected to be included in the analysis before decisions are made. **It is not meant to be a summary of all current information regarding the chemical.** Rather, the sheet provides some context to better understand the substantive material in the docket (RED chapters, registrant rebuttals, Agency responses to rebuttals, etc.) for this pesticide.

Further, in some cases, differences may be noted between the RED chapters and the Agency's comprehensive reports on the hazard identification information and safety factors for all organophosphates. In these cases, information in the comprehensive reports is the most current and will, barring the submission of more data that the Agency finds useful, be used in the risk assessments.

Jack Housenger, Acting Director
Special Review and Reregistration
Division

10/OPP#34133

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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DATE: September 18, 1997

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: **ETHION - *FQPA REQUIREMENT*- -Report of the Hazard Identification Assessment Review Committee.**

FROM: Jess Rowland Jess Rowland 9/18/97
Branch Senior Scientist,
Science Analysis Branch, Health Effects Division (7509C)

THROUGH: K. Clark Swentzel K. Clark Swentzel 9/18/97
Chairman, Hazard Identification Assessment Review Committee
Toxicology Branch II, Health Effects Division (7509C)

TO: Karen Whitby
Chief, Risk Characterization & Analysis Branch, Health Effects Division (7509C)

BACKGROUND: On September 2, 1997, the Health Effects Division's Hazard Identification Assessment Review Committee met to evaluate the toxicology data base of Ethion, with special reference to the reproductive, developmental and neurotoxicity data. These data were re-reviewed specifically to address the sensitivity of infants and children from exposure to Ethion as required by the Food Quality Protecting Act (FQPA) of 1996. The FQPA requirement was not addressed in the Reregistration Eligibility Document. The Committee's decisions are summarized below.

CC: Rick Whiting, Science Analysis Branch
Caswell File
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A. INTRODUCTION

The Health Effects Division's Hazard Identification Assessment Review Committee met to evaluate the toxicology data base of Ethion, with special reference to the reproductive, developmental and neurotoxicity data. These data were re-reviewed specifically to address the sensitivity of infants and children from exposure to Ethion as required by the Food Quality Protecting Act (FQPA) of 1996. The FQPA requirement was not addressed in the Ethion Reregistration Eligibility Document.

B. RESULTS: Evaluation of the toxicology data base indicated the following:

1. Neurotoxicity:

- In an acute delayed neurotoxicity study, no clinical or histopathological signs of neurotoxicity were seen in hens given a single oral dose of Ethion at 2792 mg/kg (LD_{50}). The Committee noted that this study did not assess for the potential of Ethion to inhibit neurotoxic esterase (NTE) in hens (MRID No. 00158376).

- No treatment-related pathological lesions of the central or peripheral nervous system were observed in the 90-day neurotoxicity study in rats, which is currently under review, or in the chronic toxicity studies in mice or rats (MRID Nos. 00148989 and 00148991).

2. Developmental Toxicity

- The developmental toxicity studies in rats and rabbits showed no evidence of additional sensitivity to young rats or rabbits following pre- or postnatal exposure to Ethion and comparable NOELs were established for adults and off-spring.

- In a developmental toxicity study, pregnant Charles River rats received oral doses of Ethion at 0, 0.2, 0.6 or 2.5 mg/kg/day on gestation days 6 through 15. For maternal and developmental toxicity, the NOEL was 0.6 mg/kg/day and the LOEL was 2.5 mg/kg/day. The LOEL was based on signs of hyperactivity in the dams (maternal) and on delayed ossification of pubes in the fetuses (developmental) (MRID No. 00131852).

- In the other developmental toxicity study , pregnant New Zealand White rabbits were given oral doses at 0, 0.6, 2.4 or 9.6 mg/kg/day during gestation days 6 through 18. For maternal toxicity the NOEL was 2.4 mg/kg/day and the LOEL was 9.6 mg/kg/day based on decreases in body weight gain, reduced food consumption and clinical signs (orange colored urine). For developmental toxicity, the NOEL was 9.6 mg/kg/day (highest dose tested, HDT); a LOEL was not established (MRID No. 00131853).

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3. Reproductive Toxicology

- In a 3-generation reproduction study, when administered in the diet at 0, 2, 4, or 25 ppm (1, 0.2 or 1.25 mg/kg/day, respectively) to Charles River rats, no increased sensitivity to pups over the adults was seen. For parental systemic toxicity, the NOEL was 0.2 mg/kg/day and the LOEL was 1.25 mg/kg/day based on significant decreases in plasma cholinesterase activity in F_1 and F_2 female adults (MRID No. 00148990). For reproductive toxicity, the NOEL was 1.25 mg/kg/day (HDT); a LOEL was not established.

4. Cholinesterase Inhibition

- In the 3-generation reproduction study, ChE activity was not measured in the F_0 parental animals and therefore, for this endpoint, a comparison could not be made with the pups. However, the dose (1.25 mg/kg/day) at which plasma ChE inhibition (ChEI) was seen in the F_1 and F_2 adult female rats in the reproduction study is comparable to the dose (2 mg/kg/day) at which ChEI was observed in adult rats in the chronic toxicity study with rats (00148991).

5. Developmental Neurotoxicity

- There are sufficient data available to adequately assess the potential for toxicity to young animals following pre-and/or post-natal exposure to Ethion. These include acceptable developmental toxicity studies in rats and rabbits and a 3-generation reproduction study in rats. In addition, no treatment-related neuropathology was seen in studies conducted in hens or rats. Therefore, based upon a weight-of-the-evidence consideration of the data base, the Committee determined that a developmental toxicity study is not required.

6. Reference Dose (RfD)

- A RfD of 0.0005 mg/kg/day was derived from the LOEL of 0.05 mg/kg/day and an Uncertainty Factor (UF) of 100. The LOEL was based on cholinergic signs observed at the lowest dose tested in human volunteers given oral doses of Ethion at 0.05, 0.075, 0.10 or 0.15 mg/kg/day for 21 days. The UF of 100 included a 10 to account for the difference in sensitivity within the human population and an additional 10 to account for the lack of a NOEL in the critical study.

7. Data Gaps

- The Committee noted that a data gap exists for an acute neurotoxicity study in rats.

C. CONCLUSIONS:

The Committee's conclusions on the Uncertainty Factors for acute and chronic dietary risk assessments are as follows:

1 Acute Dietary Risk Assessment

The endpoint selected for acute dietary risk assessment is based on clinical signs of cholinesterase inhibition observed at 0.05 mg/kg/day (LOEL) on day 19 in male volunteers. A NOEL was not established. In general, when the dose identified is a LOEL, an additional UF would be applied due to the lack of a NOEL in the critical study. In this case, however, since a human study was used and the effects seen occurred on day 19, an UF of 10 was appropriate.

Therefore, for acute dietary risk assessment, the Committee determined that **an additional UF of 10** to account for enhanced sensitivity to infants and children (as required by FQPA) **is not warranted. A Margin of Exposure of 10 is adequate** to ensure protection of this population from acute (single) exposure to Ethion for reasons specified below:

(I) The endpoint identified was cholinesterase inhibition in adult human (males) subjects.

(ii) There is no evidence of maternal or developmental toxicity attributable to an acute (single dose) *in utero* exposure of Ethion in developmental toxicity studies.

2. Chronic Dietary Risk Assessment

The endpoint selected for chronic dietary risk assessment is based on cholinergic signs observed at 0.05 mg/kg/day in human volunteers (LOEL). A NOEL was not established. An UF of 100 was applied to this LOEL; 10 to account for the difference in sensitivity within the human population and an additional 10 to account for the lack of a NOEL in the critical study. Thus an RfD of 0.0005 mg/kg/day was derived.

Therefore, for chronic dietary risk assessment, the Committee determined that **an additional UF of 10** to account for enhanced sensitivity of infants and children (as required by FQPA) **is not warranted.** The present **UF of 100 is adequate** to ensure the protection of this population from exposure to Ethion since there was no indication of increased sensitivity to young animals following pre-and/or post-natal exposure to Ethion as shown below:

(i) Developmental toxicity studies showed no increased sensitivity to fetuses as compared to maternal animals following *in utero* exposures in rats and rabbits.

(ii) A multi-generation reproduction toxicity study in rats showed no increased sensitivity to pups as compared to adults.